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EXAMINER	
TUCKER, ZACHARY C	
ART UNIT	PAPER NUMBER
1624	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	01/31/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/772,235	LI ET AL.	
	Examiner	Art Unit	
	Zachary C. Tucker	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 November 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-54* is/are pending in the application.

4a) Of the above claim(s) *54* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-53* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *06 February 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Election/Restrictions

A written Requirement for Restriction, in which an additional requirement for applicants to elect a singled disclosed specie of the elected invention was set forth, was mailed to applicants on 26 September 2006. In reply to that requirement, applicants have elected Group I, drawn to the compounds of formulae I, II and III, their compositions, and methods of use wherein **Y** is -NR10 or N, for examination. The first compound of claim 5 was indicated as the elected specie of the invention. The response states that the elections were made with traverse, and that "the examiner has not carried the burden of providing sufficient reason and/or examples to support any conclusion that the claims of the restricted groups are patentably distinct." The examiner disagrees, as it is plain to see that the broader generic claims encompass chemical compounds characterized by different heterocyclic ring systems - the heteroatoms in these ring systems are different, that is. When Y is a direct bond, one ring system results, when Y is a carbonyl group, another results, when Y is an oxygen atom, another results, and when Y is a nitrogen atom or a carbon atom, others still are the result. The number of non-overlapping ring systems within the scope of the instant claims, each of which is functionally different from the others, is quite large.

If applicants sincerely believe that all compounds embraced by the instant claims are *not* patentably distinct from one another; are *not* obvious variants of one another, as indicated by the examiner, then a definitive statement to that effect, on the record, would prompt withdrawal of the Requirement for Restriction presently at hand.

The Requirement for Restriction is proper. According to the MPEP §803, "...a serious burden on the examiner may be *prima facie* shown if the examiner shows by appropriate explanation of separate classification, or separate status in the art, or a

different field of search as defined in MPEP § 808.02. That *prima facie* showing may be rebutted by appropriate showings or evidence by the applicant." Applicant has made no rebuttal of the examiner's showing of separate classification and separate status in the art. Thus, a serious burden has been established. In fact, the showing of separate classification is sufficient to demonstrate patentable distinctness of the Groups as well.

For the elected single disclosed species of the invention, applicants indicated election of the first compound specified in instant claim 5.

Claim 54 is withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention. All compounds wherein the variable Y is other than a nitrogen atom have been withdrawn from consideration.

A search of the Y=N or -N(R_{10})- compounds of claims 1-53 was undertaken, with the election of species in mind. Prior art anticipating some of the claims at hand was found, whereupon the search was stopped, pursuant to "Markush practice" outlined in MPEP 803.02. The claims will be reexamined upon receipt of an amendment which overcomes the prior art-based rejection set forth in the following Office action.

Claim Rejections - 35 USC § 112

The following is a quotation of the first and second paragraphs of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.
>
> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

All claims 1-53 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Many points of indefiniteness arise throughout the claims. Each will be addressed. Although all claims may not be specifically addressed, all claims are included in this rejection, because all depend at least indirectly from some indefinite claim.

In claim 1, the definition of R^9, the term "heteroaralkyl" is repeated. In the definition of T, the limitation "when present" is recited. Variable T is *always* present in instant claim 1, so this language is ambiguous. Also in the definition of T, the term "lower alcohol" is not clear and well-defined. A "lower alcohol" is a substance unto itself, not a substituent in a molecule's structure. Recitation of a compound name, or class of compound name in the place of a substituent/moiety enumeration creates ambiguity in this case because it is not clear if the 'alcohol' is bonded through the oxygen atom, which would render the substituent an alkoxy group, or if bonded through a carbon atom, rendering it a hydroxyalkyl group. Claim 1 has been examined on the merits as though "lower alcohol" in the definition of T is hydroxy-lower alkyl.

In claim 5, the 4th specified compound contains a dangling valency on the sulfonamide nitrogen atom. It has been assumed that applicants intended for H- to be shown at this position.

The 3rd specified compound in claim 5 lacks a group T.

In claim 9, the first seven compounds specified lack a group T.

In claim 10, the first two compounds specified lack a T group.

Claim 14 includes the phrase "when present" in the definition of variable T. Since T is *always* present, as depicted in the molecular structure diagram of claim 14, the phraseology "T, when present" not understood. If T is optional, then a subscript for T should be in place, wherein said subscript has a value of zero or one.

The last two lines of claim 14 read: "wherein one, two, or three carbon atoms thereof can be replaced by a hetero-atom-containing moiety selected from the group consisting of: -O-, >C=O, -S-, -SO_2-, -NR_1SO_2-, -SO_2NR_1-, -NR_1- and -PO_2-." It is not clear whether this language refers to everything in the claim which precedes it, or if it only refers to the lower alkyl, cycloalkyl optionally containing at least one heteroatom, lower alkenyl, aryl, heteroaryl, aralkyl, heteroaralkyl, alkaryl, and alkylheteroaryl groups. It has been assumed in the examination that it refers only to the lower alkyl, cycloalkyl optionally containing at least one heteroatom *et cetera*.

In claims 22 and 36, the language "for inhibiting PARP activity, treating or preventing diseases or disorders" is not clear. Which diseases or disorders are intended is not defined.

Furthermore, in claims 22 and 36, which isoform of PARP it is that is inhibited by the composition and method according to those claims is not defined, rendering the scope of the claim unknown. There are at least five isoforms of PARP known, as evidenced by:

> Virag and Szabo, "The Therapeutic Potential of Poly(ADP-ribose) Polymerase Inhibitors" *Pharmacological Reviews*, vol. 54, pages 375-429 (2002).
>
> and
>
> Cosi, "New inhibitors of poly(ADP-ribose) polymerase and their potential therapeutic targets" *Expert Opinion on Therapeutic Patents*, vol. 12(7), pages 1047-1071 (2002).

These are PARP-1, PARP-2, PARP-3, vault-PAPR and tankyrase. Thus, claims 22 and 36 are indefinite because which isoform it is that is inhibited by the composition/method is not defined.

In claims 24 and 43, the phrase appearing in the latter parts thereof, "diseases or disorders relating to lifespan or proliferative capacity of cells, and diseases or disease

conditions induced or exacerbated by cellular senescence" is not understood. Exactly what group of medical conditions this language embraces is not known, nor would be known to the physician of ordinary skill. That one of ordinary skill can identify one or a few members of a class does not prove that the language employed to describe said class is *not* indefinite. The full scope of all "diseases or disorders relating to lifespan or proliferative capacity of cells, and diseases or disease conditions induced or exacerbated by cellular senescence" is not clear and well-defined.

Claims 1-53 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the compounds having the molecular structure depicted in the claim, their optical isomers, enantiomers, diasetereomers, stereoisorners and tautomers, does not reasonably provide enablement for all *prodrugs* of the compounds. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with the claims.

The Wands factors provide a guide for determining the scope of enablement provided by a given disclosure:

(A) The breadth of the claims;
(B) The nature of the invention;
(C) The state of the prior art;
(D) The level of one of ordinary skill;
(E) The level of predictability in the art;
(F) The amount of direction provided by the inventor;
(G) The existence of working examples; and
(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.
In re Wands, 858 F.2d 731,737 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)

(A) Though it might appear that the scope of instant claims 1, 14 and 15 is limited to compounds having the structures defined by formulae (I), (II) and (III), it is not. A prodrug, as defined by Bundgaard in:

> Hans Bundgaard, Design of Prodrugs, page 1. © 1985 Elsevier Science Publishers.

"is an inactive species, and therefore, once its job is completed, intact prodrug represents unavailable drug." Thus, an important requirement of prodrugs of compounds having the formula (I) is that they be pharmacologically inactive. Prodrugs come in myriad forms, and are not limited to only esters, which are most commonly cited as examples, and suggested as the preferred type of prodrug at pages 31 and 32 of the instant specification. A prodrug may be an amide, a Mannich base (imine), an acyclic precursor to a heterocyclic compound, a polymer-bound drug (either covalently or ionically), a compound of the drug covalently or ionically bound to another drug with different action or a carboxylic acid which is decarboxylated to provide the active drug. So, the scope of all prodrugs is actually quite broad. A prodrug does not depend on the identity of the pharmacologically active agent formed from the prodrug for patentability. A prodrug is not necessarily even structurally related to the compound of which it is a prodrug, since the metabolism in vivo of that compound is what provides the drug.

(B) Prodrugs of a compound having formulae (I), (II) and (III), depicted in the instant claims, is the nature of the invention.

(C) The state of the prior art with respect to the development of prodrugs is summarized in:

> Richard B. Silverman, The Organic Chemistry of Drug Design and Drug Action, pages 352400. © 1992 Academic Press, Inc.

Silverman teaches many kinds of prodrugs, including all of the types mentioned above in section "(A)." Pages 353 and 354 list eight various reasons why a prodrug would be desirable. On page 354, Silverman teaches that many prodrugs are discovered accidentally, and some are designed on the basis of known metabolic transformations. (D) The level of ordinary skill in the art is that of a medicinal chemist, holding a graduate level degree in the field and with experience in preparative organic chemistry. (E) As discovery of prodrugs is sometimes accidental, then it follows that whether a given compound will function as a prodrug or not is sometimes unpredictable. On the other hand, before a compound is designed specifically as a prodrug, one must first understand the metabolic milieu into which the presumptive prodrug is to be introduced, and must also know to what extent the compound will be metabolized. The metabolism of xenobiotics is not always predictable. A prodrug must also, by definition, be pharmacologically inactive, so one must know which modifications of the structure of the parent compound will render it inactive. Structure-activity relationships must in large part be determined empirically, although once a rule is discerned, the structure-activity of a given series of compounds becomes predictable.

Theoretically, if one of ordinary skill in the art knew all of the above variables, prodrug structure could be predicted in advance. The reality is that all of these considerations, in total, must be empirically determined when the compound in question is a novel compound, as are the compounds having formulae (I), (II) and (III).
(F) No specific guidance relating to the preparation of prodrugs of compounds according to the present invention appears in the specification. No metabolic studies of the compounds in vivo have been done and no structure-activity rules are outlined - certainly no teaching as to which modifications will afford an *inactive* compound is found in the

specification. The only place in the instant specification where the topic of prodrugs of compounds of the present invention is addressed is in the paragraph bridging pages 24 and 25. This passage provides information which would already be known to the person of ordinary skill in the medicinal chemistry arts insofar as the function of prodrugs is concerned. Converting one or more hydroxy groups into carboxylic esters is the only real chemical teaching pertaining to the preparation of prodrugs of the invention, but this strategy represents but a very small part of the total teaching which would be necessary for the skilled chemist to make the full scope of all prodrugs of formulae (I), (II) and (III) compounds.

(G) No working example of a prodrug is in the disclosure.

(H) In order for one of ordinary skill in the art to practice the full scope of the prodrugs of compounds of claims 1, 14 and 15, a complete structure activity analysis would have to be completed. The practitioner would first screen for which type of modifications of the molecular structure would render an inactive compound. Then, the metabolic studies of all of the inactive compounds would have to be completed, and compounds that are converted to active compounds of claim 1 in vivo identified. This research would potentially be inconclusive and could take years. Additionally, one of ordinary skill in the art would necessarily have to undertake an effort to make totally new compounds not bearing any structural similarity to the compounds having structure of compounds of the present invention, such as the procyclic compounds converted to heterocyclic compounds in vivo, which are mentioned on page 360 of Silverman. Work with polymeric forms of the compounds of the present invention would be necessary also. Because different animals' metabolisms differ to the extent that xenobiotics are handled by different enzymatic pathways, this effort would have to be duplicated in each species for

which a prodrug were sought. As evidence that animals will differ substantially in the manner that xenobiotics are metabolized, the examiner presents:

> Al-Dabbagh and Smith, "Species differences in oxidative drug metabolism: some basic considerations," *Archives of toxicology*. Supplement. Archly fur Toxikologie. supplement, vol. 7, pages 219-231 (1984).

Al-Dabbagh and Smith states that the metabolic process itself is highly variable both between and within animal species, and that the toxic effect of many chemicals is a function of how the chemical is metabolized rather than the substance itself.

Given the amount of direction in the disclosure, this amount of experimentation is clearly undue. Applicants have not described the manner and process of making prodrugs of compounds of the present invention, in such full, clear, concise, and exact terms as to enable any person skilled in the art to do so.

Claims 22-53 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the treatment of neural tissue damage resulting from ischemia and reperfusion injury does not reasonably provide enablement for tissue damage resulting from cell damage or death due to necrosis or apoptosis, neuronal mediated tissue damage or diseases, neurological disorders and neurodegenerative diseases, vascular stroke, cardiovascular disorders, age-related muscular degeneration, AIDS and other immune senescence diseases, arthritis, atherosclerosis, cachexia, cancer, degenerative diseases of skeletal muscle involving replicative senescence, diabetes (whether type I, II or diabetes insipidus), head trauma, immune senescence, inflammatory bowel disorders, muscular dystrophy, osteoarthritis, osteoporosis, chronic pain, acute pain, neuropathic pain, nervous insult, peripheral nerve injury, renal failure, retinal ischemia, septic shock, and skin aging, diseases or disorders relating to lifespan or proliferative

capacity of cells, and diseases or disease conditions induced or exacerbated by cellular senescence.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

As a legal authority in the determination of whether a claimed invention is enabled by the disclosure, the Office relies on the Wands factors:

(A) The breadth of the claims;
(B) The nature of the invention;
(C) The state of the prior art;
(D) The level of one of ordinary skill;
(E) The level of predictability in the art;
(F) The amount of direction provided by the inventor;
(G) The existence of working examples; and
(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

In re Wands, 858 F.2d 731,737 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)

(A) Claim 22-53 are extremely broad in scope. Cardiovascular disease includes all vascular diseases, including those caused by physical deformities; septic shock includes all types of septic shock, caused by any microorganism and any toxin; nervous insult refers to any type of damage or injury to the nervous system, peripheral or central and could include any type of neurotoxicity caused by any toxic agent; treatment of stroke includes stroke of any level of severity at any point during or after the embolic event; arthritis is a name ascribed to any joint inflammation from any cause; multiple sclerosis is a very variable condition and the symptoms depend on which areas of the nervous system have been affected; 'diabetes' could refer to Type I diabetes (insulin dependent type), Type II diabetes (non insulin dependent type) or diabetes insipidus;

renal failure refers to renal failure from any cause; head trauma refers to trauma of any severity, from any type of insult – blunt force or even gunshot wounds; 'cancer' refers to any and all cancers; and terms like 'diseases or disorders relating to lifespan or proliferative capacity of cells' or 'diseases or disease conditions induced or exacerbated by cellular senescence' are not clear and well-defined to the extent that any particular set of conditions could be thereto ascribed.

Because the scope of claims 22-53 are so broad, and because only one condition is enabled by the disclosure (treatment of neural tissue damage resulting from ischemia and reperfusion injury), this finding of lack of enablement will be framed from the point of view of what is enabled, rather than enumerating every condition which is not enabled.

(B) The nature of the invention is that of medical treatment methods, wherein the therapeutic agent is a compound whose pharmacological activity is inhibition of the enzyme poly(ADP-ribose) polymerase ("PARP").

(C) State of the art in the therapeutic application of PARP inhibitors is given by the Virág and Szabó reference, cited above. Although it is true that by 2002, PARP-1 inhibition had been suggested as a *possible* treatment strategy for many diseases, application of PARP-inhibiting agents to the treatment of no disease was state of the art at that time, much less in 1999, when the present invention was made. However, the above-cited Cosi reference, at page 1063, (last paragraph) teaches that at the time the invention was made, the evidence was strongest for a role of PARP inhibitors being of therapeutic use in treatment of ischemia and inflammation-based tissue damage (page 1063, last full paragraph). Applicants should not interpret this statement as an indication that treatment of inflammation generally, with a compound of the invention, is enabled.

Enablement for the scope of "inflammation" generally is not present. For a compound or genus of compounds to be effective against inflammation .qenerailv is contrary to medical science. Inflammation is a process which can take place in virtually any part of the body. There is a vast range of forms that it can take, causes for the problem, and biochemical pathways that mediate the inflammatory reaction. There is no common mechanism by which all, or even most, inflammations arise. Mediators include bradykinin, serotonin, C3a, C5a, histamine, assorted leukotrienes and cytokines, PARPs, and many, many others. Accordingly, treatments for inflammation are normally tailored to the particular type of inflammation present, as there is no, and there can be no "magic bullet" against inflammation generally.

Inflammation is the reaction of vascularized tissue to local injury; it is the name given to the stereotyped ways tissues respond to noxious stimuli. These occur in two fundamentally different types. Acute inflammation is the response to recent or continuing injury. The principal features are dilatation and leaking of vessels, and recruitment of circulating neutrophils. Chronic inflammation or "late-phase inflammation" is a response to prolonged problems, orchestrated by T-helper lymphocytes. It may feature recruitment and activation of T- and B-lymphocytes, macrophages, eosinophils, and/or fibrobtasts. The hallmark of chronic inflammation is infiltration of tissue with mononuclear inflammatory cells. Granulomas are seen in certain chronic inflammation situations. They are clusters of macrophages which have stuck tightly together, typically to wall something off. Granulomas can form with foreign bodies such as aspirated food, toxocara, silicone injections, and splinters.
Otitis media is an inflammation of the lining of the middle ear and is commonly caused by Streptococcus pneumoniae and HaemophUus influenzae. Cystitis is an inflammation

of the bladder, usually caused by bacteria. Blepharitis is a chronic inflammation of the eyelids that is caused by a staphylococcus. Dacryocystitis is inflammation of the tear sac, and usually occurs after a long-term obstruction of the nasolacrimal duct and is caused by staphylococci or streptococci. Preseptal cellulitis is inflammation of the tissues around the eye, and Orbital cellulitis is an inflammatory process involving the layer of tissue that separates the eye itself from the eyelid. These life-threateninginfections usually arise from staphylococcus. Hence, these types of inflammations are treated with antibiotics.

Certain types of anti-inflammatory agents, such as non-steroidal anti-inflammatory medications (Ibuprofen and naproxen) along with muscle relaxants can be used in the non-bacterial cases. The above list is by no means complete, but demonstrates the extraordinary breadth of causes, mechanisms and treatment (or lack thereof) for inflammation. It establishes that it is not reasonable to any agent to be able to treat inflammation generally.

Toxin-producing bacteria cause septic shock, not PARP, so inhibition of PARP will not afford a treatment of septic shock. Stroke is refers to an artery blockage, usually by an embolus, in the brain, so PARP inhibition will not be a treatment for stroke because such will not remove the embolus.

Nervous insults result from so many types of events that one therapeutic agent simply cannot be capable of rendering a treatment for all nervous insults.

Stroke is an event where the blood flow to a certain part of the brain is stopped, usually due to some type of embolism, usually a thromboembolism. Inhibition of the enzyme PARP could provide a means for lessening the damage caused by the resultant

ischemia and reperfusion injury, but cannot provide a means for unblocking the blocked artery.

Head trauma cannot be prevented, or treated with a chemical compound. Certain sequelae of head trauma, such as ischemia which could result from subdural hematoma, could be ameliorated by inhibition of PARP, however.

"Senescence," literally, "growing old," which is recited several times in claims 22-53, in various contexts, cannot be treated with a chemical compound. Mankind has for thousands of years tried to develop some drug, potion, or concoction which will reverse aging, and as of yet these efforts have borne no fruit. Applicants' compounds, it is reasonable to assert, cannot reverse to any extent the aging process of the immune system, skeletal muscles, or cells in general.

PARP has not been correlated with transmission of pain impulses through the nervous system, so inhibition of PARP will not provide a means for treatment of pain, whether acute or chronic.

PARP's association with cancer, and treatment of cancer, was not such that treatment of all cancers was within the level of ordinary skill at the time the present invention was made. The state of the art with respect to PARP inhibitors and treatment of cancers is exemplified by:

> Bowman et al, "Differential effects of the poly (ADP-ribose) polymerase (PARP) inhibitor NU1025 on topoisomerase I and II inhibitor cytotoxiclty in L1210 cells in vitro" British Journal of Cancer, vol. 84(1),pages 106-112 (2001).

and,

> Griffin et al, "The role of inhibitors of poly (ADP-ribose) polymerase as resistance-modifying agents in cancer therapy" Biochimie, vol. 77, pages 408-422 (1995).

and,

Worker, Charlotte "A novel PARP inhibitor, ion channel modulation and AD therapies" IDrugs, vol. 2(9), pages 859-860 (1999).

The Bowman et al reference reports that the cytotoxic effect of the PARP-I inhibitor NU1025 was quite pronounced for camptothecin (potentiated both LCs0 and LC90 by a factor of 2.6) on page 107 (in the section headed "RESULTS"), while no potentiation of cytotoxicity from etoposide was observed. Bowman et al theorizes that the observed difference is due to differences in the nature of the DNA strand breaks formed by the two drugs (page 110, column two, second full paragraph).

The Griffin et al reference (page 418, column one) reports that the dihydroisoquinoline PARP-1 inhibitor PD128763 potentiates both X-ray cytotoxicity andmonofunctional alkylating agent activity, but not BCNU (commonly known as carmustine) and CCNU (commonly known as lomustine). BCNU and CCNU are commonly employed in the treatment of brain tumors. These references teach that PARP inhibitors will increase the cytotoxicity of certain cytotoxic agents, not that PARP inhibitors alone would be sufficient to treat cancer.

Worker reports that during the EPHAR Congress meeting in 1999, a state-of-the-art PARP inhibitor, dubbed BGP-15 was described by researchers from the University Medical School of Pécs, Hungary. This compound had shown promising results in experiments relating to its ability to potentiate cytotoxic agents (adriamycin, cisplatin) while descreasing the acute toxicity thereof, in the mouse. In dogs, rats and rabbits, the drug showed good bioavailability and elimination. No therapeutic indication other than as a potentiator for chemotherapy agents in the treatment of cancer was suggested by the Hungarian researchers who developed the compound. The only cancer in which actual data were reported was leukemia.

(D) The level of ordinary skill with respect to instant claim 27 is a physician, specializing in cardiology, neurology, infectious disease, endocrinology rheumatology or oncology, depending on the disease treated.

(E) Predictability is low with respect to the claimed method. Page 417 of Virág and Szabó states flatly that further work needs to establish the exact in vivo mechanism of PARP inhibitors. It must be emphasized that data obtained from knockout mouse (PARP -/-) studies cannot always be extrapolated to situations in which pharmacological agents inhibit PARP. Each of the methods of treatment specified in the instant claims must be developed with experimental work on the part of whoever would practice it, since applicants have not done this work. That some experimentation is needed does not necessarily mean that the methods are not enabled. Those of ordinary skill, physicians who routinely treat diseases specified in the present claims, do not normally conduct the type of research which would be necessary to realize the methods specified in the claims, however.

(F) The specification provides no direction specific to the treatment of any particular disease with a compound of the present invention. No dosage range specific to any particular disease is provided, no information as to how long a course of treatment with the compounds of the invention is necessary, depending on the disease or condition being treated is present, and no teachings as to which compounds out of the many thousands embraced by formulae (I), (II) and (III) are the best for the various purposes claimed is in the specification.

(G) No example of the treatment of any disease appears in the specification. The instant specification includes some experimental data in rats supporting the claimed utility of

decreasing neural and cardiac tissue damage resulting from ischemia and reperfusion injury. Prophetic experiments wherein the ability of the compounds to decrease "altered gene expression and protein expression in mRNA senescent cells," "*in vitro* radiosensitization," and "extending or decreasing proliferative capacity of cells" are described, but these do not support the enablement of the methods according to the instant claims, as no data is actually gleaned from the experiments.

(H) Since applicants have done no experimentation relating the methods claimed in the application, all of the necessary experimentation would have to be done by one of ordinary skill. No guidance relating to the methods according to claims 36-53, or the intended uses according to claims 22-35, is provided by the instant specification. Thus, applicants have effectively limited the enablement of the claims to that which was already known to those of ordinary skill at the time the invention was made.

In order to realize the full scope of instant claims 22-53, one of ordinary skill must study every disease within the scope of the claim (as stated in section "A," there are many), and every compound embraced by formulae (I), (II) and (III), in all combinations (every disease in combination with every compound). Optimal dosages for every disease must be determined. This quantity of experimentation is undue.

Much of the subject matter embraced by claims 22-53 is impossible (treatment of all cancers, treating head trauma with a chemical agent, treatment of all neurological and/or neurodegenerative diseases, for example).

Applicants' right to exclude others from practicing the subject matter of claims 22-53 is unwarranted in light of the lack of clear direction as to how to do so.

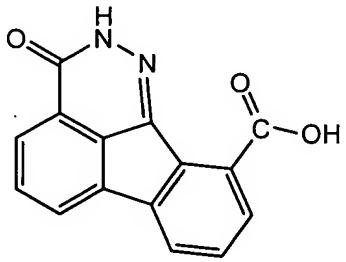
Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 14 is rejected under 35 U.S.C. 102(b) as being anticipated by Sieglitz et al, "3-Hydroxyfluoroanthene-1-, -2-, and -10-carboxylic acids" *Chemische Berichte*, vol. 95, pages 3013-3029 (1962), as abstracted by CAPLUS.

The Sieglitz et al abstract discloses a compound having the structure:



, which is embraced by instant claim 14 wherein X is a bond; both q are zero; R^9 is H, R^1 through R^7 are H; Z is O and Y is N. A full copy of the reference has been requested from the U.S.P.T.O library and is forthcoming.

Obviousness-Type Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory

double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-6, 8, 10, 12, 14 and 15 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-9, 11 and 12 of U.S. Patent No. 6,716,828. Although the conflicting claims are not identical, they are not patentably distinct from each other because the elected species for examination which is presently operative in the instant case is specified as the first compound in claim 5 of the patent, and thus is embraced by claim 1 of the patent, from which it depends. Thus, both claims 1 are overlapping in their scope. The language of claims 2, 3 and 4 in both the instant application and the patent are the same, and the language of instant claim 8 and claim 6 of the patent, instant claim 10 and claim 8 of the patent, instant claim 12 and claim 9 of the patent are all the same as well.

Instant claims 14 and 15 are identical to claims 11 and 12 of the patent, save for the definition of Y in instant claims 14 and 15, which include -CH- and $-CH_2-$, while claims 11 and 12 of the patent do not include these alternatives in the definition of Y.

Claims 16-21 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 13-18 of U.S. Patent No. 6,716,828. Although the conflicting claims are not identical, they are not patentably distinct from each other because the language of the claims is the same, and claims 13-18 of the patent depend from claim 1 thereof, which is shown in the preceding paragraphs to overlap with instant claim 1.

Claims 1, 9 and 14 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-3. Patent No. 6,291,425. Although the conflicting claims are not identical, they are not patentably distinct from each other because the compounds specified in each of claims 1, 2 and 3 of the patent (each is independent) are embraced by the independent claims in the instant application, claims 1, 14 and 15.

Both compounds specified in claim 1 of the patent, the sixth compound specified in claim 2 of the patent and the fourth compound specified in claim 3 of the patent are each embraced by claim 1 of the instant application. Claim 14 of the instant application is anticipated by claim 3 of the patent. The first compound specified in instant claim 9 is the same as the third compound specified in claim 2 of the patent.

Other claims in the instant application are rendered unpatentable by claims of the patent, but for the sake of brevity it has been assumed that applicants will be able to determine where the overlap occurs. The patent's claims are drawn solely to a series of individual compounds.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope.

The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

Instant claim 13 is rejected over claim 10 of U.S. patent number 6,716,828. Claim 10 of the patent specifies the same two compounds as does instant claim 13.

Instant claim 7 is rejected over claim 1 of U.S. patent number 6,291,425. Claim 1 of the patent is drawn to the same two compounds as is instant claim 7.

Claim Objections

Applicant is advised that should claim 16 be found allowable, claims 22-35 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

In the instant case, claims 22-35 specify the pharmaceutical composition of claim 16, wherein the composition is "for" various utilities. The intended use of a composition of matter does not result in a physical difference in that composition of matter, only a notion in the mind of whoever might be employing said composition. A mental step cannot serve as a claim limitation. The instant specification, in addition, does not teach any particular sub-genera of compounds of the present invention as being more suited to any particular utility than others.

Specification

The abstract of the disclosure is objected to because the single sentence of which it is composed is not sufficiently descriptive of the invention. Compounds which inhibit the enzyme PARP are not new. Applicants' invention is not merely 'compounds,

pharmaceutical compositions, and methods of using the disclosed compounds for inhibiting PARP." It is a group of unique (and presumably novel) chemical compounds that have the property of being able to selectively inhibit the enzyme PARP. Therefore, description of the invention, as in a patent abstract, behooves the provision of a generic structure diagram, which would provide some information as to the chemical identity of these PARP-inhibiting compounds.

A generic structural formula should be included in the abstract.

Correction is required. See MPEP § 608.01(b).

Allowable Subject Matter

The following actions by applicants would place the application in condition for allowance and ensure a speedy issuance of the patent:

Cancellation of claims 7, 13, 14 and 22-54, properly filed Terminal Disclaimers over commonly owned and invented U.S. Patent Nos. 6,291,425 and 6,716,828, deletion of "prodrugs thereof" in all occurrences, amendment of the claims as suggested so as to overcome the indefiniteness rejections, and limiting variable Y in all occurrences to –N- or $-N(R_{10})-$.

A claim drawn to a method of treating neural tissue damage resulting from ischemia and reperfusion injury, comprising administering a therapeutically effective amount of a compound of claim 1 would be allowable. Method claims which depend from such a claim, commensurate in scope with present claims 37-41 would be allowable as well.

If applicants wish, a claim drawn to treatment of cardiac tissue damage resulting from ischemia and reperfusion injury, comprising administering a compound of the

invention in a therapeutically effective amount, would be allowable. Support for such a method is found in the example in the specification bridging pages 69 and 70.

Conclusion

Any inquiry concerning this communication should be directed to Zachary Tucker whose telephone number is (571) 272-0677. The examiner can normally be reached Monday to Friday from 5:45am to 2:15pm. If Attempts to reach the examiner are unsuccessful, contact the examiner's supervisor, James O. Wilson, at (571) 272-0661.

The fax number for the organization where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

ZACHARY C. TUCKER
PRIMARY EXAMINER